Title
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Publication Date
2011

DOI
10.4061/2011/702735

Peer reviewed

SAGE-Hindawi Access to Research
Journal of Osteoporosis
Volume 2011, Article ID 702735, 4 pages
doi:10.4061/2011/702735

Review Article

The Bone-Muscle Relationship in Men and Women

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Received 30 June 2011; Accepted 10 August 2011

Academic Editor: Pawel Szulc

Muscle forces are a strong determinant of bone structure, particularly during the process of growth and development. The gender divergence in the bone-muscle relationship becomes strongly evident during adolescence. In females, growth is characterized by increased estrogen levels and increased mass and strength of bone relative to that of muscle, whereas in men, increases in testosterone fuel large increases in muscle, resulting in muscle forces that coincide with a large growth in bone dimensions and strength. In adulthood, significant age-related losses are observed for both bone and muscle tissues. Large decrease in estrogen levels in women appears to diminish the skeleton's responsiveness to exercise more than in men. In contrast, the aging of the muscle-bone axis in men is a function of age related declines in both hormones. In addition to the well-known age related changes in the mechanical loading of bone by muscle, newer studies appear to provide evidence of age- and gender-related variations in molecular signaling between bone and muscle that are independent of purely mechanical interactions. In summary, gender differences in the acquisition and age-related loss in bone and muscle tissues may be important for developing gender-specific strategies for using exercise to reduce bone loss with aging.

1. Introduction

Skeletal fractures occur when bones are subjected to mechanical loads which exceed their strength. Diminished skeletal strength is a primary risk factor for fracture, and gender differences in skeletal structure and strength play a powerful role in determining gender differences in fracture risk. Skeletal structure adapts to the long-term loads exerted on the skeleton exerted as a result of physical activity, and the most powerful loading forces are conferred by muscles, which must exert enough force to move bones while acting against extremely short lever arms. Thus, skeletal muscle is one of the most powerful determinants of bone strength and gender differences in the bone-muscle relationship are of key interest in understanding gender differences in bone growth, in age-related bone loss, and in risk of fracture. The close coupling between muscle and bone and the gender differences in the relationship are often viewed in the context of the the mechanostat theory, first elaborated by Frost [1, 2]. In this paradigm, the muscle-bone relationship, expressed as the "bone-muscle unit," is viewed as a mechanical relationship modulated by the systemic effects (e.g., hormones). Bones respond to the varying strains imposed by increases or decreases of mechanical loading, with sharp losses or modeling effects triggered when strains, respectively, fall below or exceed setpoints that are determined by the gender-specific interaction of systemic factors with bone tissue. These same endocrine factors also have direct gender-specific interactions with muscle tissues, altering muscle mass and strength and affecting the loads placed on bone. Finally, newer research points to direct two-way signaling between muscle and bone tissues, broadening the relationship beyond that of a purely mechanical perspective.

2. Gender Differences in the Bone-Muscle Unit in Childhood and Adolescence

Skeletal fragility in old age is a function of peak bone strength in young adulthood and age-related loss of bone strength.

In order to understand gender differences in fracture risk in elderly subjects, it is important to understand the gender differences in the conditions of accrual of peak bone strength during childhood and adolescence. The achievement of peak bone strength is a function both of accrual bone of mass and changes in bone geometry, and this differs strongly in males and females in relation to patterns of skeletal muscle growth.

The idea of the bone-muscle unit, derived from the mechanostat theory [1, 2], has been widely employed to account for gender-specific trends in acquisition of peak bone strength in relation to growth of muscle area [3, 4]. From this point of view, bone structure evolves to match increased tissue strains occurring as a function of growth. During the period of rapid growth in adolescence, bone structure constantly adapts to maintain stability in the presence of mechanical loads and a rapidly changing hormonal environment. In this phase, changes in mechanical loads occur as bones grow longitudinally, resulting in higher lever arms and increasing bending moments. The increasing size and strength of muscles result in larger deformation forces on bone. The increased mechanical stimulation due to the combination of longitudinal growth and muscle contraction results in bone growth primarily due to periosteal bone formation.

Gender differences in the relation of muscle and bone growth are generally not evident in early childhood, and studies show little to any differences in the relation of muscle to bone area. However, gender-variant patterns emerge during adolescence, reflecting the different musculoskeletal effects of testosterone and estrogen in males and females [5]. In males, the changes of bone and muscle during puberty are dominated by the increasing levels of testosterone and IGF-1, which result in increased muscle mass and strength. The combination of higher deformation forces and the higher bending moments due to longitudinal growth leads to a bone growth pattern dominated by periosteal apposition. Thus, in men, the growth in muscle and bone is more parallel in nature and the peak values of cortical area and muscle cross-sectional area tend to coincide within half a year in men. In girls, with lower levels of testosterone, and higher levels of estrogen, bone mass, but not total cross-sectional area, tends to increase more rapidly in relation to muscle area. The increase in bone mass appears to take the form of increased endosteal apposition, rather than periosteal apposition. A study examining gender differences in bone structure in young men and women at the hip, distal tibia, and distal radius found that men have higher total and cortical bone cross-sectional area, but volumetric density values similar to those observed in women [6]. When the data are adjusted for differences in body height, gender differences in cortical thickness and area are highly attenuated, but differences in total bone cross-sectional area remain large. The higher total bone area is consistent with higher muscle cross-sectional area found in young men compared to young women. In young adulthood, there are apparent gender differences in the correlation of muscle area to bone area. In men, more of the variation in bone dimensions is explained by muscle area in men [7]. Women have higher values of bone in relation to muscle, but a lower percentage of the variation in cortical area in women is explained by muscle mass [8].

3. Aging, Physical Activity, and Skeletal Integrity

After attainment of peak bone and muscle strength, both men and women begin to lose both bone and muscle tissue with age. In women, age-related bone loss begins in the early to mid-thirties. This process is greatly accentuated by the rapid decrease of estrogen levels occurring as a result of the menopause. Men have a lower rate of bone loss that continues throughout the lifespan that is also influenced by age-related decreases in estradiol levels. Both men and women undergo age-related muscle loss associated with decline in testosterone levels, with men undergoing a larger lifetime loss of muscle mass and strength.

In the aging process, the bone-muscle relationship is affected by gender differences in the rate of loss of bone and muscle and in the mechanosensitivity of bone. In males, aging is characterized by large declines in testosterone, and men experience cross-sectional and longitudinal losses of muscle strength and mass that are twice what is observed in women [9, 10]. Women, on the other hand, experience an over 50% larger lifetime loss of bone mass and strength, driven by loss of age- and menopause-related loss of estrogen [6, 11]. Although bone and muscle show sharply different age-related changes in men and women, the critical factor for the bone muscle relationship is the change in bone mechanosensitivity that occurs in women as a function of estrogen loss. At the cellular level, mechanical loading involves a series of molecular events that depend on the estrogen receptor alpha (ER-α). ER-α number declines with menopause, reducing the ability of mechanical loading to induce an osteogenic response [12]. This picture is consistent with gender differences in the relationship of muscle mass with bone density, with men tending to show higher correlations between muscle mass and areal bone density [13]. It is also consistent with observations that the effect of strenuous exercise on bone mineral density is attenuated in older compared to younger women and that among older subjects, evidence seems to point to more robust exercise effects on bone in men. Overall, the relationship of muscle mass to bone structure and strength is more preserved in men than in women. While exercise can be of high relevance in reducing the rate of age-related bone loss in both genders, the effect is especially important in men.

4. Muscle and Bone Tissues as Individual Targets of Systemic Hormone Action

IGF-1 is a hormone that targets both muscle and bone tissue and is considered to be of particularly high importance in the development of osteoporosis and sarcopenia in males. IGF-1 stimulates the proliferation of muscle progenitor cells and their integration with existing fibers during the muscle repair process [14]. It also affects pathways controlling the calcium-induced contractility of muscle fibers. IGF-1 is also anabolic

for bone. Mice with overexpression of IGF-1 show higher cortical tissue properties. In men, increasing IGF-1 levels are associated with increasing femoral neck density [15]. The expression of IGF-1 in muscle tissue may be associated with the positive skeletal effects of exercise in both young and elderly men, and the age-related decrease of IGF-1 levels may lead to decreased mechanosensitivity as reflected in the lower effects of exercise on bone in elderly men.

Androgens play a significant role in the development and maintenance of muscle and of skeletal integrity in both men and women. Androgens stimulate the skeletal modeling process by inhibition of RANKL action on osteoclasts both through their own receptors and through aromatization to estrogen. In the growth process, androgens are responsible for large increases in formation of trabecular bone and are in particular associated with bone size, in both men and women [16]. Androgen loss has a particularly important effect in men; eugonadal men undergo severe bone loss, which can be partially recovered through androgen replacement therapy. Androgens also have a particularly important role in skeletal muscle in men. Increased testosterone levels are associated with increased muscle mass in men, and low levels of androgen lead to loss of muscle mass and reduced growth of muscle mass in boys. Androgens are also important for skeletal and skeletal muscle development in women. Women with low testosterone levels show higher degrees of menopause-related bone loss, a condition that can be counteracted through androgen supplementation [17].

While estrogen is central to skeletal growth and maintenance of skeletal integrity in women, it is also a significant factor for men. Estrogen inhibits the action of proresorption cytokines. Decrease in estrogen levels, in both genders, results in increased bone resorption, but low levels of estrogen also affect the skeleton by decreasing mechanosensitivity. Thus, as with androgens, estrogens affect the muscle bone system by decreasing the effect of muscle contractions on bone, leading potentially to decreased efficacy of resistance exercise in men as well as women with increasing age.

5. Molecular Signaling between Muscle and Bone

Emerging research indicates that muscles release factors that are detected by bones and that may affect bone structure and strength independently of mechanical loads. In a study of mice lacking a muscle-specific phosphatase (MIP/MTMR14;MIPKO), Brotto et al. reported increases in intracellular phosphate accompanied by impaired calcium homeostasis, decreases in the function of skeletal, cardiac, and smooth muscle, as well as deterioration of trabecular structure with no effect on cortical bone [18]. The skeletal effects of ablation of MIP were gender-specific. Female knockout mice of 12–14 months showed severe trabecular bone loss, but this knockout did not appear to have a similar effect on male mice. Further investigation in this area is underway, and a potential gender difference in muscle-bone signaling, which is independent of the mechanical loads on bone exerted by muscle, may have importance for gender-specific strategies for prevention of muscle and bone loss.

6. Summary

In conclusion, the interaction between bone and muscle, in the process of growth and development and in the process of aging, differs between men and women. In females, the growth process is characterized by increased mass and strength of bone relative to that of muscle, whereas in men, increases in testosterone fuel large increases in muscle, resulting in muscle forces that coincide with a large growth in bone dimensions and strength. In both genders, aging causes pronounced losses in both tissues, but the large decrease in estrogen levels in women appears to diminish the skeleton's responsiveness to exercise more than in men. In contrast, the aging of the muscle-bone axis in men is a function of age-related declines in both hormones. The gender differences in the acquisition and age-related loss in bone and muscle tissues may be important for developing gender-specific strategies for using exercise to reduce bone loss with aging.

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